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EXAMINER	
SHAW, AMANDA MARIE	

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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	**Application No.** 10/684,134	**Applicant(s)** PADGETT ET AL.
	Examiner AMANDA SHAW	**Art Unit** 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,5,7 and 9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,5,7 and 9-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date *11/24/2008*.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed November 24, 2008. This action is made FINAL.

Claims 1-2, 4-5, 7, and 9-12 are currently pending. Claims 1, 7, and 9 have been amended.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) and 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original non-provisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosures of the prior-filed applications, CIP Applications 10/637,758, 10/226,372, 10/280,913, and 10/066,390 and Provisional Applications 60/402,342, 60/268,785, and 60/266,386, fail to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. The CIP and Provisional Applications fail to provide adequate support for the instant claims 1-2, 4-5, 7, and 9-12 because they do not teach (i) preparing a heteroduplex having at least 75% sequence identity, (ii) forming a population of polynucleotides containing sequence variants wherein at least 44% of the population has undergone reassortment wherein the sequence variants have an average of 1 or more crossovers per 95 base pairs, and (iii) forming a population of polynucleotides containing sequence variants wherein at least 20% of the population has undergone reassortment wherein the sequence variants have an average of 1 or more crossovers per 250 base pairs. Thus, the instant claims 1-2, 4-5, 7, and 9-12 have not been granted benefit of the earlier-filed CIP and Provisional Applications, and the filing date of this Application, 10/684,134 (10/10/2003) has been used for prior art purposes.

Withdrawn Rejections

3. The rejection made under 35 USC 112 2nd paragraph in section 3 of the Office Action of July 22, 2008 is withdrawn in view of amendments made to the claims.

The rejections made under 35 USC 103(a) in sections 5-6 of the Office Action of July 22, 2008 are withdrawn in view of amendments made to the claims.

Response to the Declaration

4. The declaration under 37 CFR 1.132 filed November 24, 2008 (Padgett Declaration No. 3 does not provide sufficient support for the amendments made to the claims. As such the claims have been rejected under 35 USC 112 1st paragraph (new

matter). The reasons why the declaration does not provide support for the amendments are discussed in detail below in paragraph 5.

Claim Rejections - 35 USC § 112 1st paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a new ground of rejection necessitated by amendment:

Claims 1-2, 4-5, 7, and 9-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

(A) The specification does not appear to provide support for the amendment to the claims to recite the phrase "at least 75% sequence identity". The claim language of “at least 75%” encompasses 76%, 77%, 78%, and >79%. It is noted that the applicant points to the specification (Examples 10, 15) and Padgett Declaration No: 3 for support. Example 10 describes two heteroduplexes that are “approximately 75%” identical (para 00218). Example 15 describes heteroduplexes that are “approximately 47%, 58%, 62%, and 75%” identical (para 00218). Declaration No: 3 discloses heteroduplexes that are 75%, 66%, 65%, and 54% identical. As such neither the specification nor the declaration provides specific support for "at least 75%". Further it is noted that the specification discloses heteroduplexes that are “96% identical” (para 00217) and heteroduplexes that are “about 95%, 90%, 85%, 80%, and 75% identical” (para 0016) however these teachings also do no provide specific support for heteroduplexes that are at least 75% identical.

(B) The specification does not appear to provide support for the amendment to the claims to recite the phrase "at least 44% of the population has undergone reassortment of sequence information". The claim language of “at least 44%” encompasses 45%, 46%, 47%, and >48%. It is noted that again the applicant points to the specification (Examples 10, 15) and Padgett Declaration No: 3 for support. The specification is silent with regard to the percentage of the population that has undergone reassortment of sequence information. Declaration No: 3 discloses that with regard to heteroduplexes that were 75% identical only 44% underwent reassortment of sequence information. The declaration does not teach any heteroduplexes wherein 45%, 46%, 47% or 48% underwent reassortment of sequence information. As such neither the specification nor the declaration provides specific support for "at least 44% of the population has undergone reassortment of sequence information". Further the term “reassortment” can have several different meanings (i.e. rearrangements, deletions, insertions, and substitutions) but the specification does not provide basis for this and particularly does not provide basis for the concept that at least 44% of the population includes these types of sequence rearrangements.

(C) The specification does not appear to provide support for the amendment to the claims to recite the phrase "an average of 1 or more crossovers per 95 base pairs". The claim language of “1 or more” encompasses 2, 3, 4, and >5. It is noted that again the applicant points to the specification (Examples 10, 15) and Padgett Declaration No: 3 for support. The specification is silent with regard to the average number of crossovers per base pair. Declaration No: 3 discloses that with regard to heteroduplexes that were 75% identical the average number of crossovers per kb was 10.6. This would result in an average of 1 crossover per 94.34 base pairs. As such neither the specification nor the declaration provide specific support for "an average of 1 or more crossovers per 95 base pairs"

(D) The specification does not appear to provide support for the amendment to the claims to recite the phrase "at least 20% of the population has undergone reassortment of sequence information". The claim language of “at least 20%” encompasses 21%, 22%, 23%, and >24%. It is noted that again the applicant points to the specification (Examples 10, 15) and Padgett Declaration No: 3 for support. The specification is silent with regard to the percentage of the population that has undergone reassortment of sequence information. Declaration No: 3 discloses that with regard to heteroduplexes that were 54% identical only 20% underwent reassortment of sequence information. The declaration does not teach any heteroduplexes wherein “21%, 22%, 23%, and 24%” underwent reassortment of sequence information. As such neither the specification nor the declaration provides specific support for "at least 20% of the population has undergone reassortment of sequence information". Further claims 7 and

9 do not require that the heteroduplexes have a specific percent identity, therefore the claims encompass methods wherein the percent identity is less than 54% and based on the information present in the declaration heteroduplexes that were less than 54% identical would be expected to have less than 20% reassortment. Further the term "reassortment" can have several different meanings (i.e. rearrangements, deletions, insertions, and substitutions) but the specification does not provide basis for this and particularly does not provide basis for the concept that at least 20% of the population includes these types of sequence rearrangements.

(E) The specification does not appear to provide support for the amendment to the claims to recite the phrase "an average of 1 or more crossovers per 250 base pairs". The claim language of "1 or more" encompasses 2, 3, 4, and >5. It is noted that again the applicant points to the specification (Examples 10, 15) and Padgett Declaration No: 3 for support. The specification is silent with regard to the average number of crossovers per base pair. Declaration No: 3 discloses that with regard to heteroduplexes that were 54% identical the average number of crossovers per kb was 4.2. This would result in an average of 1 crossover per 238.1 base pairs. As such neither the specification nor the declaration provides specific support for "an average of 1 or more crossovers per 250 base pairs". Further claims 7 and 9 do not require that the heteroduplexes have a specific percent identity, therefore the claims encompass methods wherein the percent identity is less than 54% and based on the information present in the declaration heteroduplexes that were less than 54% identical would be expected to have a lower rate of crossovers.

(F) It is noted for the record that Dr. Padgett's experimental data, even though allegedly based on the sequences presented in Example 15, refers to different heteroduplexes than the ones in Example 15: sequence identities of heteroduplexes in Dr. Padgett's declaration were 54, 65, 66 and 75%, whereas those presented in Example 15, (page 72), were 47, 58, 62 and 75%. In the instant case neither the specification nor the declaration provide support for the combination of at least 75% identity of the heteroduplexes, at least 44% of the population with a replaced nucleotide or other types of sequence rearrangement, and an average of 1 or more crossovers per 95 bp because the 44% of "shuffling" occurred only when the parent genes had a 75% identity (not a > 75% identity) when the assay is performed with a sequence of approximately 800 bp. Also the declaration states that "In a given experiment, small variations in experimental conditions may affect the outcome such that shuffled clone percentages and crossover frequencies may differ somewhat from what is reported here". This indicates that the particular values reported would be applicable only to the experimental conditions provided in the declaration. Therefore there is not support for methods in which these values are obtained under any experimental condition. The results presented in the declaration correspond to a very specific combination of a T4 DNA polymerase, CEL I mismatch endonuclease and an E. coli DNA ligase, whereas the claims are drawn to any system broadly comprising any polymerase, ligase and endonuclease having mismatch directed strand cleavage activity. Additionally the experimental conditions disclosed in the specification are not required by the claims and could potentially affect the number of shuffled progeny and average number of crossovers per kb of shuffled gene. Therefore the results presented in the declaration are not commensurate in scope with the claims. For these reasons the new limitations introduced into claims represent new matter.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a new ground of rejection necessitated by amendment:

7. Claims 1-2, 4-5, 7, and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moore (WO 02/24953 Pub 3/02, Filed 9/2001, Priority 9/2000) in view of Oleykowski (Nucleic Acids Research 1998).

Regarding Claims 1-2 and 4-5 Moore teaches a method for producing recombinant polynucleotides. Moore teaches providing variant homologus parental sequences and incubating the sequences under conditions which promote heteroduplex formation (pg 6, lines 2-4). Moore teaches that in one embodiment the parental heteroduplexes are at least 70% homologous and differ in at least two base pair positions that are separated by at least one complementary base pair (pg 8, lines 24-30 and Fig 4). Thus Moore teaches preparing a heteroduplex between at least two parent polynucleotides having at least 75% sequence identity wherein said heteroduplex has at least two mismatch sites separated by at least one complementary base pair. Following heteroduplex formation, the heteroduplexes are contacted with a mixture comprising a heteroduplex repair system consisting essentially of a nuclease and a polymerase (pg 11, lines 1-3). Moore teaches that any nuclease (i.e. be it an endonuclease or an exonuclease) can be used as long at it cleaves at least one polynucleotide strand in the heteroduplex (pg 12, lines 9-12). Moore teaches using a polymerase, such as T4 DNA polymerase, to replace at least one nucleotide on at least one polynucleotide strand at or near the cleavage site (pg 11, lines 27-29). Moore teaches using a ligase in order to seal the nicks present in the heteroduplex (pg 12, lines 33-34). This process generates novel sequences i.e., sequences differing in sequence composition from the variant homologous parental sequences used in a particular reaction (pg 5, lines 19-20).

Regarding claim 2 Moore teaches a method wherein the polynucleotides forming a heteroduplex are circular (pg 10, lines 16-17). Regarding Claims 4 and 5 Moore teaches a method wherein the parent sequences can encode the same protein but be present within a different organism (pg 7, lines 31-32). Thus Moore teaches a method wherein at least one heteroduplex contains a gene. Further the heteroduplex of Moore is being interpreted as a heteroduplex that contains a genome since the claims do not require that the heteroduplex contains an "entire" genome.

Moore does not teach a method wherein the nuclease that is used is an endonuclease having mismatch directed strand cleavage activity. Moore does not teach a method wherein the endonuclease cleaves at least one polynucleotide strand in the heteroduplex within six nucleotides 3' of a mismatch site as required by claim 1.

However Oleykowski teaches a method wherein a cleaving step is performed with CEL I. In the instant case CEL I is considered to be an endonuclease having mismatch directed strand cleavage activity. CEL I incises on the 3' side of the mismatch site in one of the two DNA strands in a heteroduplex (abstract).

Accordingly it would have been obvious for one of ordinary skill in the art at the time of invention to use the CEL I mismatch endonuclease taught by Oleykowski in the method of Moore. Oleykowski teaches that CEL I can detect 100% of the sequence variants present, including deletions, insertions and missense alterations and therefore one would have been motivated to include this mismatch endonuclease in the method in order to produce a more diverse population of variant polynucleotides. Further it would have been obvious to use CEL I because the substitution of one cleavage agent for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An ordinary artisan would have had a reasonable expectation of success in utilizing CEL I in the method of Moore since Oleykowski taught that the enzyme had a neutral pH optimum (page 4601, column 1) and further taught a method for its purification from celery (page 4597, column 2). Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Further Moore does not teach forming a population of polynucleotides containing sequence variants wherein at least 44% of the population has undergone reassortment of sequence information and the sequence variants have an average of 1 or more crossovers per 95 base pairs as required by claim 1.

However it would have been prima facie obvious for one of ordinary skill in the art at the time of invention to optimize the concentrations of the endonuclease, polymerase and ligase enzymes when practicing the method of Moore and Oleykowski. An ordinary artisan would have recognized that these results-effective variables could be optimized in order to produce the desired result (*e.g.* a population wherein 44% has undergone reassortment and wherein the sequence variants have an average of 1 or more crossovers per 95 base pairs). As noted in MPEP 2144.05, the routine optimization of results-effective variables is *prima facie* obvious in the absence of secondary considerations. Further Moore teaches that the instant invention is used for generating recombinant sequences with enhanced features relative to the parent sequences (pg

14, lines 10-12). Therefore one would be motivated to optimize the method in order to generate a larger population (i.e. at least 44%) of polynucleotides that have undergone reassortment because there is a higher chance of finding a polynucleotide that actually has an enhanced feature.

Regarding Claim 7 Moore teaches a method for producing recombinant polynucleotides. Moore teaches providing variant homologus parental sequences and incubating the sequences under conditions which promote heteroduplex formation (pg 6, lines 2-4). Moore teaches that in one embodiment there are preferably at least two parental sequences (which encompasses 3, 4, 5, etc parental sequences) which differ in at least two base pair positions that are separated by at least one complementary base pair (pg 8, lines 24-30 and Fig 4). Thus Moore teaches preparing at least two heteroduplexes among at least three parent polynucleotides wherein each different heteroduplex has at least two mismatch sites separated by at least one complementary base pair. Following heteroduplex formation, the heteroduplexes are contacted with a mixture comprising a heteroduplex repair system consisting essentially of a nuclease and a polymerase (pg 11, lines 1-3). Moore teaches that any nuclease (i.e. be it an endonuclease or an exonuclease) can be used as long at it cleaves at least one polynucleotide strand in the heteroduplex (pg 12, lines 9-12). Moore teaches using a polymerase, such as T4 DNA polymerase, to replace at least one nucleotide on at least one polynucleotide strand at or near the cleavage site (pg 11, lines 27-29). Moore teaches using a ligase in order to seal the nicks present in the heteroduplex (pg 12, lines 33-34). This process generates novel sequences i.e., sequences differing in sequence composition from the variant homologous parental sequences used in a particular reaction (pg 5, lines 19-20).

Moore does not teach a method wherein the nuclease that is used is an endonuclease having mismatch directed strand cleavage activity. Moore does not teach a method wherein the endonuclease cleaves at least one polynucleotide strand in the heteroduplex within six nucleotides 3' of a mismatch site as required by claim 7.

However Oleykowski teaches a method wherein a cleaving step is performed with CEL I. In the instant case CEL I is considered to be an endonuclease having mismatch directed strand cleavage activity. CEL I incises on the 3’ side of the mismatch site in one of the two DNA strands in a heteroduplex (abstract).

Accordingly it would have been obvious for one of ordinary skill in the art at the time of invention to use the CEL I mismatch endonuclease taught by Oleykowski in the method of Moore. Oleykowski teaches that CEL I can detect 100% of the sequence variants present, including deletions, insertions and missense alterations and therefore one would have been motivated to include this mismatch endonuclease in the method in order to produce a more diverse population of variant polynucleotides. Further it would have been obvious to use CEL I because the substitution of one cleavage agent for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An ordinary artisan would have had a reasonable expectation of success in utilizing CEL I in the method of Moore since Oleykowski taught that the enzyme had a neutral pH optimum (page 4601, column 1) and further taught a method for its purification from celery (page 4597, column 2). Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Moore does not teach forming a population of polynucleotides containing sequence variants wherein at least 20% of the population has undergone reassortment of sequence information and the sequence variants have an average of 1 or more crossovers per 250 base pairs as required by claim 7.

However it would have been prima facie obvious for one of ordinary skill in the art at the time of invention to optimize the concentrations of the endonuclease, polymerase and ligase enzymes when practicing the method of Moore and Oleykowski. An ordinary artisan would have recognized that these results-effective variables could be optimized in order to produce the desired result (*e.g.* a population wherein 20% has undergone reassortment and wherein the sequence variants have an average of 1 or more crossovers per 250 base pairs). As noted in MPEP 2144.05, the routine optimization of results-effective variables is *prima facie* obvious in the absence of secondary considerations. Further Moore teaches that the instant invention is used for generating recombinant sequences with enhanced features relative to the parent sequences (pg 14, lines 10-12). Therefore one would be motivated to optimize the method in order to generate a larger population (i.e. at least 20%) of polynucleotides that have undergone reassortment because there is a higher chance of finding a polynucleotide that actually has an enhanced feature.

Regarding Claims 9-12 Moore teaches a method for producing recombinant polynucleotides. Moore teaches providing variant homologus parental sequences and incubating the sequences under conditions which promote heteroduplex formation (pg 6, lines 2-4). Moore teaches that in one embodiment the parental heteroduplexes differ in at least two base pair positions that are separated by at least one complementary base pair (pg 8, lines 24-30 and Fig 4). Thus Moore teaches preparing a heteroduplex between at least two parent polynucleotides wherein said heteroduplex has at least two mismatch sites separated by at least one complementary base pair. Following heteroduplex formation, the heteroduplexes are contacted with a mixture comprising a heteroduplex repair system consisting essentially of a nuclease and a polymerase (pg 11, lines 1-3). Moore teaches that any nuclease (i.e. be it an endonuclease or an exonuclease) can be used as long at it cleaves at least one polynucleotide strand in the heteroduplex (pg 12, lines 9-12). Moore teaches using a polymerase, such as T4 DNA polymerase, to replace at least one nucleotide on at least one polynucleotide strand at or near the cleavage site (pg 11, lines 27-29). Moore teaches using a ligase in order to seal the nicks present in the heteroduplex (pg 12, lines 33-34). This process generates novel sequences i.e., sequences differing in sequence composition from the variant homologous parental sequences used in a particular reaction (pg 5, lines 19-20). Moore further teaches screening or selecting said population for a desired functional property (pg 14, lines 4-6). Regarding Claim 10 Moore teaches that mutants bearing different beneficial point mutations discovered in one round of directed evolution can be shuffled (pg 14, lines 17-20). Thus Moore teaches a method further comprising forming a second heteroduplex containing at least one variant polynucleotide strand, cleaving the mismatch, replacing the nucleotide, and screening or selecting a population of variant for a desired functional property. Regarding Claims 11 and 12 Moore teaches that the recombined polynucleotides can be inserted into a vector, which is then inserted into a host for expression. The host cells are then screened to identify clones containing the desired mutations (pg 13, lines 15-20). Moore further teaches that an enzyme possessing a particular function or level of function can be tested by measuring or identifying the actual function of the recombinant protein (pg 14, lines 4-6). As such Moore teaches a method comprising translating the variant polynucleotide or an RNA transcribed therefrom to produce a polypeptide wherein screening or selecting is performed on said polypeptide.

Moore does not teach a method wherein the nuclease that is used is an endonuclease having mismatch directed strand cleavage activity. Moore does not teach a method wherein the endonuclease cleaves at least one polynucleotide strand in the heteroduplex within six nucleotides 3' of a mismatch site as required by claim 9.

However Oleykowski teaches a method wherein a cleaving step is performed with CEL I. In the instant case CEL I is considered to be an endonuclease having mismatch directed strand cleavage activity. CEL I incises on the 3’ side of the mismatch site in one of the two DNA strands in a heteroduplex (abstract).

Accordingly it would have been obvious for one of ordinary skill in the art at the time of invention to use the CEL I mismatch endonuclease taught by Oleykowski in the method of Moore. Oleykowski teaches that CEL I can detect 100% of the sequence variants present, including deletions, insertions and missense alterations and therefore one would have been motivated to include this mismatch endonuclease in the method in order to produce a more diverse population of variant polynucleotides. Further it would have been obvious to use CEL I because the substitution of one cleavage agent for another would have yielded predictable results to one of ordinary skill in the art at the time of the invention. An ordinary artisan would have had a reasonable expectation of success in utilizing CEL I in the method of Moore since Oleykowski taught that the enzyme had a neutral pH optimum (page 4601, column 1) and further taught a method for its purification from celery (page 4597, column 2). Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Moore does not teach forming a population of polynucleotides containing sequence variants wherein at least 20% of the population has undergone reassortment of sequence information and the sequence variants have an average of 1 or more crossovers per 250 base pairs as required by claim 9.

However it would have been prima facie obvious for one of ordinary skill in the art at the time of invention to optimize the concentrations of the endonuclease, polymerase and ligase enzymes when practicing the method of Moore and Oleykowski. An ordinary artisan would have recognized that these results-effective variables could be optimized in order to produce the desired result (*e.g.* a population wherein 20% has undergone reassortment and wherein the sequence variants have an average of 1 or more crossovers per 250 base pairs). As noted in MPEP 2144.05, the routine optimization of results-effective variables is *prima facie* obvious in the absence of secondary considerations. Further Moore teaches that the instant invention is used for generating recombinant sequences with enhanced features relative to the parent sequences (pg 14, lines 10-12). Therefore one would be motivated to optimize the method in order to generate a larger population (i.e. at least 20%) of polynucleotides that have undergone reassortment because there is a higher chance of finding a polynucleotide that actually has an enhanced feature.

Conclusion

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw
Examiner
Art Unit 1634

/Carla Myers/
Primary Examiner, Art Unit 1634